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## **REMARKS**

### **I. Status of the Claims**

Claims 1-16 were previously pending in the application with claims 1 and 6 being the independent claims. Claims 1, 6-8, 11, and 15 have been amended.

Support for the amendments to the specification and to the claims can be found in the application (including the specification, figures, claims) as originally filed, such as on pages 7-24, in the Examples, and in the original and amended claims.

Support for the amendments to claims 1, 6-8, 11, and 15 can be found throughout the specification as originally filed, particularly on pages 7-12. Additional support for the amendments to claims 1 and 6 can be found on page 7, lines 21-30 and on page 8, lines 1-2. Additional support for the amendments to claims 7 and 8 can be found on page 7, lines 25-30, and on page 8, lines 1-2. Additional support for the amendments to claims 11 and 15 can be found on page 7, lines 21-30 and on page 8, lines 3-8.

### **II. Status of the Claims**

Claims 1-16 were previously pending in the present application. In the Office Action, mailed 17 November 2003, the Examiner rejected claims 1-16.

Currently, claims 1-16 are pending in the application. Claims 1, 6-8, 11, and 15 have been amended.

### **III. The Acknowledgement of the Priority Claim to the Provisional Application**

The Examiner has acknowledged the priority claim of the present application to U.S. Provisional Application No. 60/175,307 (filed January 10, 2000). Applicants thank the Examiner for acknowledging the priority claim.

#### **IV. The Objection to the Specification is Accommodated in Part and Traversed in Part**

The Examiner has objected to the specification on several grounds, which will be addressed in two groups.

##### **A. The Objection to the Disclosure due to Informalities is Accommodated**

The Examiner has objected to the disclosure due to informalities concerning the number of examples and the sequence listing (paragraphs 2A, 2B, and 6).

Applicants have submitted a substitute specification (marked and unmarked copies) herewith to accommodate the Examiner's objections. A Statement That the Substitute Specification Contains No New Matter has also been provided.

The Examiner has objected to the specification, because it contains multiple sets of examples "not numbered in one series" (par. 2A). As a result of the Examiner's request for incorporation of material into the specification (Office Action, mailed March 26, 2002), material from two applications had been quoted in the body of the specification. The numbering of the examples is amended in the Substitute Specification submitted herewith in order to accommodate the Examiner's present objection. Example numbers in the quoted passages have been indicated with brackets in accordance with standard practice to indicate amendments to quoted material. Example numbers in non-quoted passages have simply been amended.

The Examiner has requested correction of the specification as having “been found to contain multiple Sequence Listings..., while only one is permitted” (par. 2B).

The Examiner also alleges:

The amendment filed 11 March 2003 is objected to because it does not include a new Sequence Listing, a new Computer Readable form of said Sequence Listing, and a statement that "the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing" and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b) or 1.825(d). A statement that the sequence listing information is identical is required. (Par. 6.)

As a result of the Examiner's request for incorporation of material into the specification (Office Action, mailed March 26, 2002), material from two applications had been quoted in the body of the specification, including the sequence listing pertaining to one of the applications (see Amendment filed September 26, 2002, and the Substitute Specification filed March 5, 2003). An electronic sequence was provided with the Amendment filed September 26, 2002, along with a Statement. The Substitute Specification filed March 5, 2004. The quoted sequence listing has been removed and then added to the overall sequence listing for the present application, with the appropriate amendment of the sequence identifier number in the quoted material, in the Substitute Specification submitted herewith in order to accommodate the Examiner's present objection. The amended sequence identifiers in the quoted passages have been indicated with brackets in accordance with standard practice to indicate amendments to quoted material. A new sequence listing is provided herewith, along with an electronic copy and a statement.

Applicants respectfully submit that the amendments to the numbering of the examples and to the sequence listing hereby accommodate the Examiner's objections to the specification and respectfully submit that these amendments to the specification place the application in condition for allowance.

**B. The Objections to the Specification Concerning Incorporation by Reference is Traversed**

1. The Objection Alleging Improper Incorporation by Reference is Traversed

The Examiner has objected to the specification “as documents have been improperly incorporated by reference” (paragraph 1; see also paragraphs 3-5).

The Examiner quotes *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d 1673, 1679 at length:

Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6<sup>th</sup> Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Par. 1; italics in original; bold emphasis added by Examiner.)

Applicants respectfully traverse the Examiner's rejection.

First, it should be noted that in *In re Seversky* (474 F.2d at 673-74), the U.S. Court of Customs & Patent Appeals reviewed three related applications, namely, a “grandparent” application, a continuation-in-part “parent” application, and a continuation-in-part of the parent application, with respect to disclosure of a Venturi gas inlet. The grandparent application disclosed the Venturi gas inlet, but the parent application neither directly disclosed the Venturi gas inlet, nor expressly stated that it incorporated the disclosure of the grandparent by reference. In holding that the Venturi gas inlet of the grandparent application was not incorporated by reference, the court stated:

...Appellant admits to this defect in the parent application....He urges, however, that the defect is cured because the grandparent...discloses a Venturi inlet and because the parent application is a “continuation-in-part” of the grandparent that disclosure is, ipso facto, “incorporated by reference” in the parent.

**It should be noted in this connection that the parent application...contains no “incorporation-by-reference” language whatsoever. Its only relation to [the grandparent] is indicated by the simple statement that it is a “continuation-in-part” thereof.** That language is insufficient to incorporate any part of [the grandparent] into the parent case. All it means is that insofar as the disclosure *of the parent* finds corresponding disclosure in the grandparent, the parent is entitled to the filing date of the grandparent. 35 U.S.C. §120. *In re Seversky*, 474 F.2d at 673-74 (italics in original; bold emphasis added).

Second, it should be noted that in *In re Lund*, 376 F.2d at 989, the U.S. Court of Customs & Patent Appeals was concerned with whether the Examiner could use an example in the parent application as an anticipatory disclosure of a continuation-in-part patent during prosecution of another patent application when there was neither sufficient disclosure in the CIP application nor an express statement that it incorporated the disclosure of the parent by reference. In holding that the example disclosed in the parent application was not incorporated by reference, the court stated:

....As the expression itself implies, the purpose of ‘incorporation by reference’ is to make one document become a part of another document by referring to the former in the latter in such a manner that it is apparent that the cited document is part of the referencing document as if it were fully set out therein.

Here, however we do not think that the single sentence by which [CIP applicant] refers to his earlier application – ‘The present application is a continuation-in-part application of our application Serial No. 763,806, filed September 29, 1958 (now abandoned)’ – is sufficient in and of itself to render Example 2 of the abandoned [parent] application part of the patent disclosure as if fully set out therein. 376 F.2d at 989 (emphasis added).

Applicants respectfully assert that the cases cited by the Examiner are distinguishable from the situation with respect to the present application.

The specification states:

In the practice of the invention, cDNA molecules or cDNA libraries are produced by mixing one or more nucleic acid molecules obtained as described above, which is preferably one or more mRNA molecules such as a population of mRNA molecules, with one or more polypeptides having reverse transcriptase activity under conditions favoring the reverse transcription of the nucleic acid molecule by the action of the enzymes to form one or more cDNA molecules (single-stranded or double-stranded). Thus, the method of the invention comprises (a) mixing one or more nucleic acid templates (preferably one or more RNA or mRNA templates, such as a population of mRNA molecules) with one or more reverse transcriptases and (b) incubating the mixture under conditions sufficient to make one or more nucleic acid molecules complementary to all or a portion of the one or more templates. Such methods may include the use of one or more DNA polymerases. The invention may be used in conjunction with methods of cDNA synthesis such as those described in the Examples below, or others that are well-known in the art [references omitted], to produce cDNA molecules or libraries. **In a preferred embodiment, the cDNA may be produced using the methods detailed in United States patent application serial number 09/076,115 and/or United States provisional application serial number 60/122,395 filed March 2, 1999.** (P. 19, ll. 9-31; bold and underlined emphasis added; references omitted.)

First, unlike the grandparent and parent applications in *In re Seversky* and *In re Lund*, respectively, the applications cited in the present application are expressly incorporated by reference. Unlike the incorporation-by-reference statement in the present application, the “one sentence reference” in *In re Lund* does not include an express incorporation by reference of the parent application – merely a statement concerning priority.

Second, the incorporation-by-reference statement of the present application is set forth in a manner generally approved by the USPTO. Such a sentence may be found in a great many issued patents, which would have to be invalidated if a more detailed statement were required.

Third, the incorporation-by-reference statement in the present application is not simply a bald statement of incorporation-by-reference, but rather refers the reader to a method for producing cDNA.

In view of the foregoing remarks, Applicants respectfully assert that the documents have been not been improperly incorporated by reference. Therefore, Applicants respectfully request reconsideration and withdrawal of the Examiner's objection to the specification.

## 2. The Objection Alleging Introduction of New Matter is Traversed

The Examiner also objects to the specification under 35 U.S.C. §132 "because it introduces new matter into the disclosure" (par. 3).

The Examiner alleges:

....35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is as follows: That portion of the specification added to marked-up pages 20-89, 98-99, and 102.

Acknowledgement is made of where at page 3 of the Office in the Office action mailed 26 March 2002 the specification was objected to as essential subject matter had been incorporated by reference. While applicant has undertaken efforts to bring such subject matter into the present application, that material deemed essential to enabling the present application was not properly incorporated by reference, as the original specification did not "clearly indicate where that material is found in the various documents". See *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679, *supra*.

Applicant is required to cancel the new matter in the reply to this Office Action. (Pars. 3-5.)



Applicants respectfully disagree for reasons already expressed *supra*.

As noted, the incorporation-by-reference statement in the present application is not simply a bald statement of incorporation-by-reference, but rather refers the reader to a method for producing cDNA.

Moreover, Applicants again traverse the statement that the subject matter incorporated by reference is “essential.”

Applicants note that, in pertinent part, the specification states:

In the practice of the invention, cDNA molecules or cDNA libraries are produced by mixing one or more nucleic acid molecules obtained as described above, which is preferably one or more mRNA molecules such as a population of mRNA molecules, with one or more polypeptides having reverse transcriptase activity under conditions favoring the reverse transcription of the nucleic acid molecule by the action of the enzymes to form one or more cDNA molecules (single-stranded or double-stranded). Thus, the method of the invention comprises (a) mixing one or more nucleic acid templates (preferably one or more RNA or mRNA templates, such as a population of mRNA molecules) with one or more reverse transcriptases and (b) incubating the mixture under conditions sufficient to make one or more nucleic acid molecules complementary to all or a portion of the one or more templates. Such methods may include the use of one or more DNA polymerases. **The invention may be used in conjunction with methods of cDNA synthesis such as those described in the Examples below, or others that are well-known in the art** (*see, e.g., Gubler, U., and Hoffman, B.J., Gene 25:263-269 (1983); Krug, M.S., and Berger, S.L., Meth. Enzymol. 152:316-325 (1987); Sambrook, J., et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, pp. 8.60-8.63 (1989); and WO 98/51699*), to produce cDNA molecules or libraries. In a preferred embodiment, the cDNA may be produced using the methods detailed in United States patent application serial number 09/076,115 and/or United States provisional application serial number 60/122,395 filed March 2, 1999. (P. 19, ll. 9-31; italics in original; bold emphasis added.)

Applicants submit that Examples 21 and 22 (Examples 4 and 5 in the application as filed) provide descriptions of cDNA synthesis. The results of the experiments in Example 21 (formerly Example 4) are shown in Figures 2-4 and are discussed in the specification, and the

results of the experiments in Example 22 (formerly Example 5) are discussed in the specification. In addition, the methods noted in the Examples use commercially available kits. Both examples are also found in U.S. Provisional Application 60/175,307, filed January 10, 2000.

In pertinent part, Example 21 (formerly Example 4) provides:

*RT-PCR.* Using a HARRIS MICRO-PUNCH®, 2-mm punches were transferred to 1.5 ml low-binding RNase-free DNase-free tubes (Marsh Biomedical) containing 400 µl of RNA processing buffer (10 mM Tris-HCl pH 8.0, 0.1 mM EDTA, 400 - 800 U/ml RNASEOUT® and 2 mM DTT) and incubated on ice for 25 min with vortexing every 5 min.. In some experiments, the processing buffer also contained 250 µg/ml glycogen to facilitate subsequent precipitation of the RNA. Unlike genomic DNA, RNA elutes from the filter punches during this incubation. RT-PCR was done either directly using the processing buffer eluate as substrate or using RNA precipitated from the eluate. The RNA was precipitated by addition of salt (0.1 volumes of 3 M sodium acetate, or 0.5 volumes of 7.5 M ammonium acetate) and 0.5 volumes of ice cold 100% isopropanol. The samples were placed at -20°C overnight, spun down at 12,000 rpm in the microfuge, washed with 75% ethanol (ice-cold) and allowed to air dry. RNA pellets were resuspended in 50 µl or 100 µl of sterile TE. **Synthesis of first strand cDNA was performed using SUPERScript® It RNase H-RT (Life Technologies, Inc) in a final volume of 50 µl at 50°C. Amplification reactions (50 µl) contained ≤ 10 µl of the cDNA reaction and the following: 1X Amplification Buffer, 1.8 mM MgSO<sub>4</sub>, 200 nM primers, 200 mM of each dNTP and 2.5 U of PLATINUM® Taq DNA polymerase. For templates larger than 4 kb, 1-2U of PLATINUM® Taq DNA Polymerase High was used.** Amplification products were analyzed by 1.2% TBE-OR 0.8% TAE agarose gel electrophoresis.

The results of the amplification of nucleic acids stored on solid supports are shown in Figures 2-4....(P. 96, ll. 1-25; italics in original; bold emphasis added.)

Applicants respectfully submit that both methods and the ensuing results have been provided in the present application<sup>1</sup> and in the priority provisional application.

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<sup>1</sup> Applicants note that the amendments of typographical errors from “ml” to “µl” in the Examples are fully supported by the text of the provisional application as filed and that one of ordinary skill in the art would understand that “µl” would be appropriate for cDNA synthesis and that the “µl” units were intended.

In addition, Applicants provided a number of references, including Sambrook et al. (a standard reference well-known to those of ordinary skill in the art), describing additional methods for producing cDNA.

Applicants respectfully submit that no essential new matter has been introduced into the specification.

Applicants are confused by the Examiner's allegations of new matter with respect to pages 98-99 and 102.

With respect to pages 98-99, Applicants wish to draw the Examiner's attention to the marked copy of the Substitute Specification submitted on March 5, 2003, more specifically to a comparison of the paragraph added at page 98, line 23, to page 99, line 18, with the paragraph deleted at page 99, line 18, to page 100, line 13. With respect to page 102, Applicants wish to draw the Examiner's attention more specifically to a comparison of the paragraph added at page 102, lines 8-25, with the paragraph deleted at page 102, line 25, to page 103, line 11. The Examiner will readily note that in both instances the "added" paragraphs contain sequence identifiers in compliance with the rules concerning sequence listings, while the "deleted" paragraphs do not. The "additions" were made in an effort to bring the application into conformity with the rules concerning sequence listings. To cancel these paragraphs would remove the sequence identifiers required by the rules. If the Examiner believes that further additional matter has been improperly introduced, Applicants respectfully request the Examiner to describe the alleged new matter disclosed in these paragraphs more specifically.

Again, Applicants respectfully traverse the Examiner's objections regarding the introduction of new matter into the specification under 35 U.S.C. §132. Therefore, Applicants respectfully request reconsideration and withdrawal of the Examiner's objection to the specification.

**V. Objections to the Claims are Accommodated**

The Examiner has objected to the claims as follows:

A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

A claim, which depends from a dependent claim, should not be separated by any claim that does not also depend from said dependent claim. In the present case, claims 8-12 and 16 are separated from independent claim by claims 6 and 7, of which claim 6 is an independent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

Claim 11 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 requires that the "solid medium" be a "matrix," however, the material recited in claim 11 effectively broadens the scope of claim 1 to where the "solid medium" is something other than a "matrix."

Applicant is advised that should claim 12 be found allowable, claim 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same-thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). (Pars. 7-10.)

The claims submitted with the previously submitted Substitute Specification, filed March 5, 2003, were in the same order as those properly submitted in the Amendment filed September 26, 2002. Claims 1-7 were originally in the specification. In the Amendment filed on September 26, 2002, claims 1-7 were amended and new claims 8-16 were added, resulting in the separation of dependent claims in accordance with procedures for entering new claims after the last old claim and not renumbering the claims. Applicants had retained the numbering of the Amendment in the previously submitted Substitute Specification to avoid confusion.

Therefore, to avoid any additional confusion, Applicants have requested the Examiner to enter the presently submitted Substitute Specification and only then to amend the claims in

accordance with the present Amendment. In this way, the new claims will follow the last of the original claims in the standard format for amendment.

Claim 11 has been amended to accommodate the Examiner's remarks. Claim 15 has been similarly amended.

With respect to the Examiner's objections to claim 16 in view of claim 12, if claim 12 is allowed, Applicants will review claim 16 accordingly. Because claim 12 has not yet been allowed, Applicants respectfully submit that cancellation of claim 16 is not necessary at this time.

In view of the foregoing remarks, Applicants submit that the Examiner's objections have been accommodated. Therefore, Applicants respectfully request reconsideration and withdrawal of the Examiner's objection to the claims.

**VI. Rejection of Claims 1-16 Under 35 U.S.C. § 112, First Paragraph, is Traversed**

The Examiner rejected claims 1-16 under 35 U.S.C. 112, first paragraph, as "failing to comply with the written description requirement."

The Examiner alleged:

....The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain

how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

As presented above, the specification has been found to be replete with new matter, and that the new matter added cannot be relied upon to support the written description requirement of 35 USC 112, first paragraph. **A review of the remaining or not affected portions of the disclosure fails to provide an adequate written description of the claimed method of producing one or more cDNA molecules so as to reasonably suggest that applicant, at the time of filing, was in possession of the invention.** Accordingly, and in the absence of convincing evidence to the contrary, claims 1-16 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. (Pars. 12-13; italics in original; bold emphasis added.)

Applicants respectfully disagree. In particular, Applicants traverse the Examiner's arguments that the specification is "replete with new matter" and that "the remaining or not affected portions of the disclosure fails to provide an adequate written description of the claimed method of producing one or more cDNA molecules so as to reasonably suggest that applicant, at the time of filing, was in possession of the invention." Applicants traverse the Examiner's characterization of the added portions of U.S.S.N. 09/076,115 and U.S. Provisional Application 60/122,395 as "new matter."

In the interests of furthering prosecution, however, Applicants note that, in pertinent part, the specification states:

In the practice of the invention, cDNA molecules or cDNA libraries are produced by mixing one or more nucleic acid molecules obtained as described above, which is preferably one or more mRNA molecules such as a population of mRNA molecules, with one or more polypeptides having reverse transcriptase activity under conditions favoring the reverse transcription of the nucleic acid molecule by the action of the enzymes to form one or more cDNA molecules (single-stranded or double-stranded). Thus, the method of the invention comprises (a) mixing one or more nucleic acid templates (preferably one or more RNA or mRNA templates, such as a population of mRNA molecules) with one or more reverse transcriptases and (b) incubating the mixture under conditions sufficient to make one or more nucleic acid molecules complementary to all or a portion of the one or more templates. Such methods may include the use of one or more DNA polymerases. **The invention may be used in conjunction with**



**methods of cDNA synthesis such as those described in the Examples** below, or others that are well-known in the art [references omitted], to produce cDNA molecules or libraries. In a preferred embodiment, the cDNA may be produced using the methods detailed in United States patent application serial number 09/076,115 and/or United States provisional application serial number 60/122,395 filed March 2, 1999. (P. 19, ll. 9-31; bold emphasis added; references omitted.)

Applicants submit that Examples 21 and 22 (Examples 4 and 5 in the application as filed) provide descriptions of cDNA synthesis. The results of the experiments in Example 21 (formerly Example 4) are shown in Figures 2-4 and are discussed in the specification, and the results of the experiments in Example 22 (formerly Example 5) are discussed in the specification. The methods additionally refer to the use of commercially available kits. Both examples are also found in U.S. Provisional Application 60/175,307, filed January 10, 2000.

In pertinent part, Example 21 (formerly Example 4) provides:

*RT-PCR.* Using a HARRIS MICRO-PUNCH®, 2-mm punches were transferred to 1.5 ml low-binding RNase-free DNase-free tubes (Marsh Biomedical) containing 400 µl of RNA processing buffer (10 mM Tris-HCl pH 8.0, 0.1 mM EDTA, 400 - 800 U/ml RNASEOUT® and 2 mM DTT) and incubated on ice for 25 min with vortexing every 5 min.. In some experiments, the processing buffer also contained 250 µg/ml glycogen to facilitate subsequent precipitation of the RNA. Unlike genomic DNA, RNA elutes from the filter punches during this incubation. RT-PCR was done either directly using the processing buffer eluate as substrate or using RNA precipitated from the eluate. The RNA was precipitated by addition of salt (0.1 volumes of 3 M sodium acetate, or 0.5 volumes of 7.5 M ammonium acetate) and 0.5 volumes of ice cold 100% isopropanol. The samples were placed at -20°C overnight, spun down at 12,000 rpm in the microfuge, washed with 75% ethanol (ice-cold) and allowed to air dry. RNA pellets were resuspended in 50 µl or 100 µl of sterile TE. **Synthesis of first strand cDNA was performed using SUPERScript® It RNase H-RT (Life Technologies, Inc) in a final volume of 50 µl at 50°C. Amplification reactions (50 µl) contained ≤ 10 µl of the cDNA reaction and the following: 1X Amplification Buffer, 1.8 mM MgSO<sub>4</sub>, 200 nM primers, 200 mM of each dNTP and 2.5 U of PLATINUM® Taq DNA polymerase. For templates larger than 4 kb, 1-2U of PLATINUM® Taq DNA Polymerase High was used.** Amplification products were analyzed by 1.2% TBE-OR 0.8% TAE agarose gel electrophoresis.

The results of the amplification of nucleic acids stored on solid supports are shown in Figures 2-4....(P. 96, ll. 1-25; italics in original; bold emphasis added.)

Applicants respectfully submit that both methods and their ensuing results have been provided in the present application<sup>2</sup> and in the priority provisional application. Clearly Applicants were “in possession of the invention” at the times when both the present application and the priority provisional application were filed.

In view of the foregoing remarks, Applicants respectfully assert that the present invention complies with the written description requirement. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-16 made under 35 U.S.C. § 112, first paragraph.

**VII. Rejection of Claims 6-8 Under 35 U.S.C. § 112, Second Paragraph, Is Traversed, but Accommodated by Amendment**

The Examiner has rejected claims 6-8 under 35 U.S.C. § 112, second paragraph, “as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention” (paragraphs 14-17).

The Examiner has rejected the use of the term “weak” in claims 7 and 8, alleging that “the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention” (par. 16).

Applicants traverse the rejection, but have accommodated the Examiner’s rejection by amendment of claims 7 and 8 to remove the term “weak” solely in the interests of furthering prosecution.

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<sup>2</sup> See footnote 1.



The Examiner has rejected the use of the term “substantially” in claim 6 as being “a relative term that renders the claim indefinite” (par. 17). The Examiner alleges that “[t]he term ‘substantially’ is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention” (par. 17).

Applicants traverse the rejection. According to Webster’s Ninth New Collegiate Dictionary (1990), the word “substantial” is defined:

**sub-stan-tial... 1 a** : consisting of or relating to substance **b** : not imaginary or illusory: REAL, TRUE **c** : IMPORTANT, ESSENTIAL **2** : ample to satisfy and nourish: FULL... **3 a** : possessed of means: WELL-TO-DO **b** : considerable in quantity: significantly large... **4** : firmly constructed: STURDY **5** : being largely but not wholly that which is specified.... (p. 1176; bold in original; underline added.)

A copy of this entry is enclosed for the Examiner’s convenience.

Applicants traverse the rejection, but have accommodated the Examiner’s rejection by amendment of claim 6 to remove the term “substantially” solely in the interests of furthering prosecution.

In view of the foregoing remarks, Applicants respectfully assert that the present invention is not indefinite. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 6-8 made under 35 U.S.C. § 112, second paragraph.

#### **VIII. Rejection of Claims 1, 2, 4, 10- 12, and 16 Under 35 U.S.C. § 102(e) (pre-AIPA) Is Traversed and Rendered Moot**

The Examiner has rejected claims 1, 2, 4, 10-12, and 16 under 35 U.S.C. 102(e) (pre-AIPA) as being anticipated by Hornes et al. (U.S. Patent No. 5,759,820; granted 6/2/98; filed 7/25/94) (paragraphs 18-23). This rejection is respectfully traversed.

The Examiner alleges that "Hornes et al., columns 6-8, disclose binding of mRNA to a solid support and then subjecting the isolated/immobilized mRNA to a reverse transcriptase so to produce a corresponding cDNA. The aspect of synthesizing a double-stranded cDNA is also disclosed therein."

Previously, Applicants noted (Amendment filed September 26, 2002) that "the mRNA of the claimed invention is not hybridized to probes, which are themselves attached to the solid medium or support. Rather, the mRNA is sorbed to the solid medium (e.g., as in claims 1, 2, and 4). The present invention does not require an insoluble support that includes magnetic particles, a coating comprising oligo-dA to reduce non-specific binding, or an attached oligonucleotide (e.g., oligo-dT)."

After discussing this point, the Examiner currently alleges:

....It is noted with particularity that the claimed method does not specify how the mRNA is sorbed to the solid medium. Accordingly, the claim has been interpreted as encompassing both direct and indirect sorption. Accordingly, indirect sorption is fairly interpreted as encompassing the sorption of mRNA to a probe that is in turn bound to the solid medium.

While agreement is reached in that the claimed method does "not require an insoluble support that includes magnetic particles, a coating comprising oligo-dA to reduce non-specific binding, or an attached oligonucleotide (e.g., oligo-dT)," the claims method also does not exclude same. Accordingly, the claimed method has been interpreted as fairly encompassing such embodiments. Accordingly, and in the absence of convincing evidence to the contrary, the rejection is maintained. (Par. 22-23.)

Applicants traverse the Examiner's rejection, but assert that the present language of claim 1 renders the Examiner's rejection moot. Applicants respectfully submit that Hornes does not describe a composition for inhibiting degradation of mRNA. Claims 2, 4, 10-12, and 16 are dependent on claim 1 or on claims that are dependent on claim 1, and the same reasoning applies to these claims as well.

In view of the foregoing remarks, Applicant respectfully asserts that the present invention is not anticipated by Hornes. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejections of claims 1, 2, 4, 10-12, and 16 made under 35 U.S.C. § 102(e).

**IX. Rejection of Claims 1-5, 10-12, and 16 Under 35 U.S.C. § 102(b) Is Traversed, but Rendered Moot**

The Examiner has rejected claims 1-5, 10-12, and 16 under 35 U.S.C. 102(b) as being anticipated by Pharmacia Biotech Catalog (1994) (paragraphs 24-27). This rejection is respectfully traversed.

The Examiner alleges:

Pharmacia Biotech Catalog (1994), page 119, discloses for sale spin columns that are packed with oligo-dT cellulose and that these solid mediums are used in methods whereby mRNA is isolated and cDNA is subsequently produced therefrom. Said cDNA is disclosed as being used in amplification assays such as PCR.

The aspect of producing a library of cDNA is disclosed in the figure seen on page 119 where a range of cDNA sizes are produced from a variety of cellular sources...

At pages 84-85 of the response received March 11, 2003, applicant reiterates the traversal placed against the use of Horne et al., in the above rejection. While agreement is reached in that the prior art does use a matrix solid (cellulose) medium that has bound to its surface oligo-dT binding moiety, the claimed method does not exclude such embodiments. Accordingly, the prior art is considered to fairly anticipate the claimed invention. (Par. 26-27.)

Applicants traverse the Examiner's rejection, but assert that the present language of claim 1 renders the Examiner's rejection moot. Applicants respectfully submit that Pharmacia Biotech Catalog (1994) does not describe a composition for inhibiting degradation of mRNA. Claims 2-5, 10-12, and 16 are dependent on claim 1 or on claims that are dependent on claim 1, and the same reasoning applies to these claims as well.

In view of the foregoing remarks, Applicant respectfully asserts that the present invention is not anticipated by Pharmacia Biotech Catalog (1994). Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejections of claims 1-5, 10-12, and 16 made under 35 U.S.C. § 102(b).

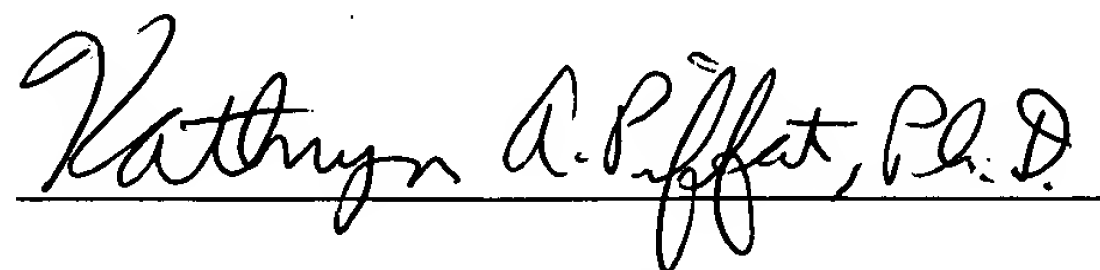
## X. Conclusion

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

Applicants hereby request a three-month extension of time for the Amendment and accompanying materials. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,



Date: April 30, 2004

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**PORT** ~ vi 1: to sign one's name to a document 2 a: to give consent or approval to something written by signing (found him unwilling to ~ to the agreement) b: to set one's name to a paper in token of promise to give something (as a sum of money); also: to give something in accordance with such a promise c: to enter one's name for a publication or service; also: to receive a periodical or service regularly on order d: to agree to purchase and pay for securities esp. of a new offering (subscribed for 1000 shares) 3: to feel favorably disposed (I ~ to your sentiments) *syn* see **ASSENT** — **sub-scrib-er** n

**sub-script** \səb-'skript/ n [L *subscriptus*, pp. of *subscribere*] (1895): a distinguishing symbol (as a letter or numeral) written immediately below or below and to the right or left of another character — **sub-script** adj

**sub-scrip-tion** \səb-'skrip-shən/ n [ME *subscripcioun* signature, fr. L *subscription-*, *scriptio*, fr. *scriptus*, pp.] (15c) 1 a: the act of signing one's name (as in attesting or witnessing a document) b: the acceptance (as of ecclesiastical articles of faith) attested by the signing of one's name 2: something that is subscribed: as a: an autograph signature; also: a paper to which a signature is attached b: a sum subscribed 3: an arrangement for providing, receiving, or making use of something of a continuing or periodic nature on a prepayment plan: as a: a purchase by prepayment for a certain number of issues (as of a periodical) b: application to purchase securities of a new issue c: a method of offering or presenting a series of public performances

**subscription TV** n (ca. 1954): pay-TV that broadcasts programs directly over the air to customers provided with a special receiver — called also *subscription television*; compare **PAY-CABLE**

**sub-section** \səb-'sek-shən/ n (1621) 1: a subdivision or a subordinate division of a section 2: a subordinate part or branch

**sub-se-quence** \səb-'sə-kwən(t)s, -si-'kwən(t)s/ n (1500): the quality or state of being subsequent; also: a subsequent event

**sub-se-quence** \səb-'sə-kwən(t)s, -sē-, -kwən(t)s/ n (ca. 1942): a mathematical sequence that is part of another sequence

**sub-se-quent** \səb-'si-'kwənt, -sə-'kwənt/ adj [ME, fr. L *subsequent-*, *subsequens*, pp. of *subsequi* to follow close, fr. *sub-* near + *sequi* to follow — more at **SUE**] (15c): following in time, order, or place: **SUCCESSING** — **subsequent** n — **sub-se-quent-ly** \-'kwənt-lē, -kwənt-\ adv — **sub-se-quent-ness** \-'kwənt-, -kwənt-\ n

**sub-serve** \səb-'sərv/ vt [L *subservire* to serve, be subservient, fr. *sub-* + *servire* to serve] (1661) 1: to promote the welfare or purposes of 2: to serve as an instrument or means in carrying out

**sub-ser-vi-ence** \səb-'sər-vē-ən(t)s/ n (1676) 1: a subservient or subordinate place or function 2: obsequious servility

**sub-ser-vi-en-cy** \-ən-sē/ n (1651): **SUBSERVIENCE**

**sub-ser-vi-ent** \-ənt/ adj [L *subservient-*, *subserviens*, pp. of *subservire*] (1632) 1: serving to promote some end 2: useful in an inferior capacity: **SUBORDINATE** 3: obsequiously submissive: **TRUCKLING** — **sub-ser-vi-ent-ly** adv

*syn* **SUBSERVIENT**, **SERVILE**, **SLAVISH**, **OBSEQUIOUS** mean showing or characterized by extreme compliance or abject obedience. **SUBSERVIENT** implies the cringing manner of one very conscious of a subordinate position (domestic help was expected to be properly *subservient*) **SERVILE** suggests the mean or fawning behavior of a slave (a political boss and his entourage of *servile* hangers-on) **SLAVISH** suggests abject or debased servility (the *slavish* status of migrant farm workers) **OBSEQUIOUS** implies fawning or sycophantic compliance and exaggerated deference of manner (waiters who are *obsequious* in the presence of celebrities)

**sub-set** \səb-'set/ n (1902): a set each of whose elements is an element of an inclusive set

**sub-shrub** \-'shrəb, esp *Southern* -səb/ n (1851): a perennial plant having woody stems except for the terminal part of the new growth which is killed back annually; also: a low shrub

**sub-side** \səb-'sid/ vi **sub-sid-ed**; **sub-sid-ing** [L *subsidiere*, fr. *sub-* + *sidere* to sit down, sink; akin to L *sedere* to sit — more at **SIT**] (1646) 1: to sink or fall to the bottom: **SETTLE** 2: to tend downward: **DESCEND**; esp: to flatten out so as to form a depression 3: to let oneself settle down: **SINK** (*subsided* into a chair) 4: to become quiet or less (as the fever ~s) (my anger *subsided*) *syn* see **ABATE** — **sub-si-dence** \səb-'sid-'n(t)s, -səb-'səd-ən(t)s/ n

**sub-si-di-ary** \səb-'sid-ē-, -er-ē, -'sid-ə-rē/ adj [L *subsidiarius*, fr. *subsidiarius* reserve troops] (1543) 1 a: furnishing aid or support: **AUXILIARY** (~ details) b: of secondary importance: **TRIBUTARY** (a ~ stream) 2: of, relating to, or constituting a subsidy (a ~ payment to an ally) — **sub-si-di-ary-ly** \-'sid-ē-'er-ə-lē/ adv

**subsidiary** n, pl -i-aries (1603): one that is subsidiary; esp: a company wholly controlled by another

**sub-si-dize** \səb-'sə-diz-, -zə-/ vt **-dized**; **-diz-ing** (1795): to furnish with a subsidy: as a: to purchase the assistance of by payment of a subsidy b: to aid or promote (as a private enterprise) with public money (~ a steamship line) — **sub-si-di-za-tion** \səb-'səd-ə-'zā-shən, -zəd-/ n — **sub-si-diz-er** n

**sub-si-dy** \səb-'səd-ē-, -zəd-/ n, pl -dies [ME, fr. L *subsidium* reserve troops, support, assistance, fr. *sub-* near + *sedere* to sit — more at **SIT**] (14c): a grant or gift of money: as a: a sum of money formerly granted by the British Parliament to the crown and raised by special taxation b: money granted by one state to another c: a grant by a government to a private person or company to assist an enterprise deemed advantageous to the public

**sub-sist** \səb-'sist/ vb [LL *subsistere* to exist, fr. L, to come to a halt, remain, fr. *sub-* + *sistere* to come to a stand; akin to L *stare* to stand — more at **STAND**] vi (1549) 1 a: to have existence: **BE** b: **PERSIST**, **CONTINUE** 2: to have or acquire the necessities of life (as food and clothing); esp: to nourish oneself (~ing on roots, berries and grubs) 3 a: to hold true b: to be logically conceivable as the subject of true statements ~ vt: to support with provisions

**sub-sis-tence** \səb-'sis-tən(t)s/ n [ME, fr. LL *subsistentia*, fr. *subsistent-*, *subsistens*, pp. of *subsistere*] (15c) 1 a (1): real being: **EXISTENCE** (an abstraction without real ~) (2): the condition of remaining in existence: **CONTINUATION**, **PERSISTENCE** b: an essential characteristic quality of something that exists c: the character possessed by whatever is logically conceivable 2: means of subsisting: as a: the minimum (as of food and shelter) necessary to support life b: a source or means of obtaining the necessities of life — **sub-sis-tent** \-'tənt/ adj

**subsistence farming** n (1937) 1: farming or a system of farming that provides all or almost all the goods required by the farm family use without any significant surplus for sale 2: farming or a system of farming that produces a minimum and often inadequate return to the farmer — called also *subsistence agriculture* — **subsistence farmer** n

**sub-so-cial** \səb-'sō-shəl, 'səb-\ adj (ca. 1909): incompletely social: esp: tending to associate gregariously but lacking fixed or complex social organization (~ insects)

**sub-soil** \səb-'soil/ n (1799): the stratum of weathered material that underlies the surface soil

**subsoil** vt (1840): to turn, break, or stir the subsoil of — **sub-soil-er** n

**sub-so-lar point** \səb-'sō-lər-/ n (1908): the point on the surface of the earth or a planet at which the sun is at the zenith

**sub-son-ic** \səb-'sän-ik, 'səb-\ adj [ISV] (1942) 1: of, relating to, or being a speed less than that of sound in air 2: moving, capable of moving, or utilizing air currents moving at a subsonic speed 3: *INFRASONIC* 1 — **sub-son-i-cal-ly** \-'i-k(ə)-lē/ adv

**sub-space** \səb-'spās/ n (1927): a subset of a space; esp: one that has the essential properties (as those of a vector space or topological space) of the including space

**sub-spe-cial-ty** \səb-'spesh-əl-tē, 'səb-\ n (1926): a subordinate field within a specialty (as in medicine)

**sub-spe-cie ae-ter-ni-ta-tis** \səb-'spek-ē-, -ī-, -ter-nə-'tāt-əs/ adv [NL, lit., under the aspect of eternity] (1895): in its essential or universal form or nature

**sub-spe-cies** \səb-'spē-shēz, -sēz/ n [NL] (1699): a subdivision of a species: as a: a taxonomic category that ranks immediately below a species and designates a morphologically or physiologically distinguishable and geographically isolated group whose members interbreed successfully with those of other subspecies of the same species where their ranges overlap b: a named subdivision (as a race or variety) of a taxonomic species — **sub-spe-cif-ic** \səb-'spi-'sif-ik/ adj

**sub-stage** \səb-'stāj/ n (1888): an attachment to a microscope by means of which accessories (as mirrors, diaphragms, or condensers) are held in place beneath the stage of the instrument

**sub-stance** \səb-'stān(t)s/ n [ME, fr. MF, fr. L *substantia*, fr. *substant-*, *substans*, pp. of *substare* to stand under, fr. *sub-* + *stare* to stand — more at **STAND**] (14c) 1 a: essential nature: **ESSENCE** b: a fundamental or characteristic part or quality c *Christian Science*: **GOD** 1b 2 a: ultimate reality that underlies all outward manifestations and change b: practical importance: **MEANING**, **USEFULNESS** (the ~ bill — which will be without ~ in the sense that it will authorize nothing more than a set of ideas — Richard Reeves) 3 a: physical material from which something is made or which has discrete existence b: matter of particular or definite chemical constitution 4: material possessions: **PROPERTY** (a man of ~) — **sub-stance-less** \-'ləs/ adj — in **substance**: in respect to essentials: **FUNDAMENTALLY**

**substance P** n (1942): a protein present esp. in the gastrointestinal tract and pituitary gland that causes reduction in blood pressure and contraction of smooth muscle and that is thought to function as a neurotransmitter

**sub-stand-dard** \səb-'stān-dərd, 'səb-\ adj (1897): deviating from or falling short of a standard or norm: as a: of a quality lower than that prescribed by law b: conforming to a pattern of linguistic usage existing within a speech community but not that of the prestige group in that community — compare **NONSTANDARD** c: constituting a greater than normal risk to an insurer

**sub-stand-tial** \səb-'stān-chəl/ adj (14c) 1 a: consisting of or relating to substance b: not imaginary or illusory: **REAL**, **TRUE** c: **IMPORTANT**, **ESSENTIAL** 2: ample to satisfy and nourish: **FULL** (a ~ meal) 3 a: possessed of means: **WELL-TO-DO** b: considerable in quantity: significantly large (earned a ~ wage) 4: firmly constructed: **STURDY** 5: being largely but not wholly that which is specified (a ~ lie) — **substantial** n — **sub-stand-tial-ity** \-'stān-chē-'al-ə-tē/ n — **sub-stand-tial-ly** \-'stān-ch(ə)-lē/ adv — **sub-stand-tial-ness** \-'stān-chəl-nəs/ n

**sub-stand-tia** n, pl -tiae \səb-'stān-chē-'ā-'nī-grə-, -'nig-rə/ n, pl **sub-stand-tiae** \-'chē-, -ē-'nī-(l)grē-, -'nig-(l)grē/ [NL, lit., black substance] (ca. 1885): a layer of deeply pigmented gray matter situated in the mid-brain and containing the cell bodies of a tract of dopamine-producing nerve cells whose secretion tends to be deficient in Parkinson's disease

**sub-stand-ti-ate** \səb-'stān-chē-'āt/ vt **-ated**; **-at-ing** (1657) 1: to give substance or form to: **EMBODY** 2: to establish by proof or competent evidence: **VERIFY** (~ a charge) *syn* see **CONFIRM** — **sub-stand-ti-a-tion** \-'stān-chē-'ā-shən/ n — **sub-stand-ti-a-tive** \-'stān-chē-'āt-iv/ adj

**sub-stand-ti-val** \səb-'stān-'ti-vəl/ adj (1832): of, relating to, or serving as a substantive — **sub-stand-ti-val-ly** \-'və-lē/ adv

**sub-stand-tive** \səb-'stān-tiv/ n [ME *substantif*, fr. MF, fr. *substantif*, adj., having or expressing substance, fr. LL *substantivus*] (14c): **NOU** broadly: a word or word group functioning syntactically as a noun — **sub-stand-tiv-ize** \-'tiv-, -iz/ vt

**sub-stand-tive** \səb-'stān-tiv; 2c & 3 also səb-'stānt-iv/ adj [ME, fr. LL *substantivus* having substance, fr. L *substantia*] (15c) 1: being a totally independent entity 2 a: real rather than apparent: **FIRM**; also: **PERMANENT**, **ENDURING** b: belonging to the substance of a thing: **ESSENTIAL** c: expressing existence (the ~ verb is the verb to be) d: requiring or involving no mordant (a ~ dyeing process) 3 a: having the nature or function of a grammatical substantive (a ~ phrase) b: relating to or having the character of a noun or pronominal term in logic 4: considerable in amount or numbers: **SUBSTANTIAL** 5: creating and defining rights and duties (~ law) 6: having substance: involving matters of major or practical importance to all concerned (~ discussions among world leaders) — **sub-stand-tive-ly** adv — **sub-stand-tive-ness** n

**substantive right** n (1939): a right (as of life, liberty, property, or reputation) held to exist for its own sake and to constitute part of the normal legal order of society

**sub-sta-tion** \səb-'stā-shən/ n (1890) 1: a branch post office 2: a subsidiary station in which electric current is transformed

**sub-sti-tu-ent** \səb-'stich-(ə-)wənt/ n [L *substituent-*, *substituens*, pp. of *substituere*] (1895): an atom or group that replaces another atom or group in a molecule — **substituent** adj

**sub-sti-tut-able** \səb-'stə-, (t)yūt-ə-bəl/ adj (1805): capable of being substituted — **sub-sti-tut-abil-ity** \səb-'stə-, (t)yūt-ə-'bil-ə-tē/ n

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